Review of Adverse Events Associated with Propoxyphene Containing Products

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
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Joann H. Lee, Pharm.D.
Division of Pharmacovigillance II

Fatmatta Kuyateh, M.D., M.S.
Division of Epidemiology

Office of Surveillance and Epidemiology

Outline

- Adverse Event Reporting System (AERS)
  - Strengths and Limitations
- AERS Reviews (1969-2005, 2006-07) and Literature Review of Cardiotoxicity
  - Overall Summary
  - 1st AERS Review: Search Criteria and Findings
  - 2nd AERS Review: Search Criteria and Findings
  - Literature Review of cardiotoxicity
  - Conclusion

Adverse Event Reporting System (AERS)

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AERS: Spontaneous Adverse Event Reporting

- Voluntary, “spontaneous” reporting
- Facilitated by the FDA MedWatch Program
- Reports are stored and retrieved via Adverse Event Reporting System (AERS) database

AERS Strengths

- Includes all U.S. marketed products
- Detection of events not seen in clinical trials
- Especially good for events with rare background rate, short latency

AERS Limitations

- Extensive underreporting
- Quality of reports is variable
- Reporting biases
- Actual numerator & denominator not known
- Causality of drug-event association often in question

Overall Summary

Summary: 1st AERS Review Darvocet (1969 to 2005)

Deaths (n=91)

- **Majority (90%) of deaths related to drug overdoses and suicides involving multiple drugs**
- **No other notable trends or characteristics**
- **A causal role of Darvocet could not be determined in any of the cases given the co-morbidities and polypharmacy**

Summary: 2nd AERS Review (n=65)

- 40% Elderly (psychiatric notable)
- 18% Fatalities (accidental overdose)
- 17% Cardiac (82% confounded)

- Possible drug-event association
  - -strong temporal relationship (16)
  - -positive dechallenges (8)
- Causality questionable based on co-morbidities and multiple drug use

Summary: Literature Review (Cardiotoxicity)

- Mostly anecdotal reports
- Lacked sufficient scientific evidence to support an association between propoxyphene-containing products and cardiotoxicity

AERS Reviews

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1st AERS Review

- **Search Criteria**
  -Search dates (1969 to 2/2/2005)
  -Trade Darvocet
  -Death as an outcome
  -US reports only

- **Search Results** (n=91)

- **Main Finding**
  -Causal role of Darvocet could not be determined given the co-morbidities and polypharmacy

2nd AERS Review: Crude Count (n=3038)

Top 20 Adverse Event Terms (US, All Events, 1969 to 9/24/2008, n=3038)			
Preferred Term (PT)	PT Counts	Preferred Term (PT)	PT Counts
Completed Suicide	433	Nausea	122
Intentional Overdose	341	Respiratory Arrest	109
Overdose	319	Vomiting	107
Multiple Drug Overdose	191	Cardio-Respiratory Arrest	104
Drug Dependence	168	Dizziness	98
Cardiac Arrest	161	Drug Interaction	94
Accidental Overdose	159	Convulsion	79
Coma	154	Confusional State	75
Drug Ineffective	130	Pulmonary Oedema	75
Drug Toxicity	126	Hypotension	74

Crude counts may contain duplicate reports and there is no certainty that the reported suspect product(s) caused the reported adverse event(s). Total Deaths (n=1452)

2nd AERS Review (2006-07)

Search Criteria

- Search dates (1/1/2006 – 12/31/2007)
- Drug names (all trade and generic single ingredient and combination products)
- Serious* outcomes only
- US cases only

Search Results

- 192 reports retrieved

*Serious per regulatory definition includes death, hospitalization or prolongation of hospitalization, life-threatening, disability, congenital anomaly, and other medically important events (CFR 314.80)

Excluded Cases (n=127) (2006-07)

Reasons for exclusion	N
Completed suicides	43
Intentional overdose/suicide attempt	11
Drug dependence/abuse/misuse	17
Duplicate reports	44
Others*	12

*Event unlikely related to propoxyphene products (9), medication error (1), miscoded (1), homicide case (1)

Demographics, Indication and Dose (2006-07)

Number of cases		65
Gender (n=63):	Male Female	21 42
Age:	Median Range	62 years (n=53) 19-92 years
Indication (n=31)		Pain (13), back pain (6), dental/surgical pain (3), joint/hip pain (3), leg/knee pain (2), osteoarthritis (2), ankle pain (1), nerve pain (1)
Total daily dose:	Median Range	200 mg (n=13) 100 mg to 800 mg

Time to Onset, Duration and Outcome (2006-07)

Estimated time to onset: Median Range	1 day (n=18) 1 dose to 4 years
Estimated duration of therapy: Median Range	 15 days (n=16) 1 day to 16 years
Outcome	Death (12), Hospitalization (29), Life Threatening (5), Other {med significant} (38)

2nd AERS Review 2006-07 (n=65)

- 45% of the cases reported confounding factors

  - contributing medical history
  - use of labeled concomitant medications

2nd AERS Review 2006-07 (n=65)

- 18% (12/65) Psychiatric related disorders

  - mental status changes-6, hallucination-5, confusional state-3, abnormal behavior-1

- 17% (11/65) Cardiac related events

  - bradycardia-4, cardio-resp arrest-2, tachycardia-2, arrhythmia-1, CHF-1, MI-1

2nd AERS Review 2006-07 (n=65)

- 15% (10/65) Drug ineffective
- 14% (9/65) Accidental multiple drug overdose
- 35% (23/65) Other adverse events
  - majority (78%) of cases reported another drug as the primary suspect drug

Cardiotoxicity Literature Review

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Literature Review Search Results

PubMed and EMBASE (1960 – 2008)

- **16 publications**
  - **3 epidemiology studies**
    - **2 randomized trials and**
    - **1 observational study**
  - **12 case reports**
  - **1 case series**

Study Findings - Mixed

- Changes in cardiac conduction not related to study medications
- Observed significant changes in cardiac conduction AND
- Correlation between conduction changes and estimated propoxyphene dose
- Cardiac Output changes not clinically significant

Limitations of Studies

- Small sample sizes
- Patients on multiple medications
- Difficulty measuring propoxyphene concentrations
- Sample populations may not represent typical users
- Negative finding DOES NOT EQUATE TO no association between propoxyphene and cardiotoxicity

Conclusion

- 1st AERS Review: causal role of propoxyphene products could not be established
- 2nd AERS Review: potential drug to event association in some cases
  - Reports were qualitatively similar to the prior AERS review
  - Causal role of propoxyphene was questionable
- Literature lacked sufficient data to establish cardiotoxicity with use of propoxyphene products
- Despite current propoxyphene label warnings, narcotic pain relievers and CNS related drugs continue to be prescribed and used with propoxyphene containing products resulting in accidental and intentional deaths.

BACK UP SLIDES

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